hybridize to their fully complementary targets, support for this amendment being found in the specification in the working exemplification.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**." Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Objections

Claims 51, 52 and 55 were objected to for failing to further limit the claims from which they depend. It is believed that this objection may arise from a misunderstanding of a phrase appearing in Claim 50. Claim 50 recites that the target nucleic acids are contacted with:

"a collection of substrate bound probe nucleic acid features that includes at least one background nucleic acid feature that is an empirically observed inactive probe that does not hybridize to a fully complementary fluorescently labeled target nucleic acid as determined in an assay wherein said probe is provided in an array that is contacted with said fluorescently labeled fully complementary target under said hybridization conditions."

The collection of substrate bound probe nucleic acids may or may not be an array of such features. The phrase " as determined in an assay wherein said probe is provided in an array that is contacted with said fluorescently labeled fully complementary target nucleic acid under said hybridization conditions" merely modifies the nature of the background feature and does not mean that the claimed method necessarily includes use of a fully complementary fluorescently labeled target or that an array is employed. In other words, this phrase merely further describes the inactive probe feature by defining it in terms of how it acts in an assay in which it is present on an array and contacted with a complementary fluorescently labeled target.

As such, Claims 51 and 52 which further specify when the target nucleic acids are labeled during the assay do further limit the method of Claim 50. Likewise, Claim 55 which positively states that the collection is an array does further limit Claim 50.

Since Claims 51, 52 and 55 do further limit Claim 50, the Examiner is respectfully requested to withdraw this objection.

Rejections

Claims 50-59, 71, 74-80 and 83-84 have been rejected under 35 U.S.C. § 112, 1st ¶, for an asserted lack of enablement with respect to failure to specify labeling and/or washing steps. Solely in order to expedite allowance of the present application, all of the claims have been modified to specifically recite such steps. The above amendments should in no way be construed as an agreement by the Applicant with the Examiner that the claims were not enabled prior to the above amendments, and the Applicant expressly reserves the right to pursue claims of the pre-amendment scope in a related continuation application.

In view of the above amendments, it is respectfully submitted that the rejection of Claims 50-59, 71, 74-80 and 83-84 under 35 U.S.C. § 112, 1st ¶ may be withdrawn.

Claims 50-57 and 60 have been rejected under 35 U.S.C. § 112, 2nd ¶ for issues with respect to Claims 50 and 60 for lack of antecedent basis for a certain term present therein. In view of the above amendments, this rejection may be withdrawn.

Claims 50-59, 71, 74-80 and 83-84 have been rejected under 35 U.S.C. § 112, 2nd ¶ for being allegedly incomplete. In view of the above amendments, this rejection may be withdrawn.

Finally, Claims 50-68 and 71-84 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Dehlinger in view of Fodor, Blanchard and Brink. In making this rejection, the Examiner asserts that since Dehlinger suggests the use of negative control probes, Fodor and Blanchard disclose arrays of all possible oligomers of the lengths of probes of the present invention, and that Brink discloses the use of type I and type II control sequences, the subject claims are obvious.

However, it is respectfully submitted that the combined teachings of the references fail to teach or suggest at least the following element of the claims.

As can be seen from Claims 50-57, 60-61 and 64-65 (as well an any dependent claims thereon), the background feature of the claims is one that does not hybridize to its fully complementary target nucleic acid under stringent conditions, where the target nucleic acid is one that is fully complementary to the probe and therefore would be expected to hybridize to the probe. As such, but for the empirical observation that the probe does not actually bind to its fully complementary target, one would expect the probe to bind to its target.

None of the references teach or suggest, either alone or in combination, such a probe as a background probe. In fact, all of the mentioned negative control probe sequences in the cited references are ones that, based on known structure and sequence, are expected not to bind to their corresponding targets. For example, the type I probes in Brink are ones that are identical in sequence to their target but of opposite polarity. Prior to actual testing, such a sequence would be known not to hybridize to its corresponding target. Similarly, Brink's Type II probe is one that has the complementary sequence to its target but has the same polarity, i.e., the two sequences are complementary only if they are lined up or paired in the same direction, i.e., 5' to 3'. For example, where a target sequence in Brink is 5'-ATCG-3', the Brink Type II probe would have a sequence 5'-TAGC-3'. When these complementary strands of the same polarity are aligned, one obtains:

5'-ATCG-3'

3'-CGAT-5'

which clearly do not hybridize to each other. Again, prior to actual testing, such a sequence would be known not to hybridize to its target.

In contrast, the background probes of these presently pending claims are ones that are empirically observed to not hybridize to their targets, where but for the empirical testing, they would be expected to hybridize to their targets under stringent conditions.

With respect to Claims 58, 62 and 66 (as well as any claims dependent thereon), these claims require the presence of specific sequences as background features, i.e., one or more of SEQ ID NOs: 05-32. Nothing in the cited references teaches or suggests that one must include these specific sequences. While Blanchard and Fodor may suggest a large number of sequences, there is no guidance in these references, or any of the other references, to select any of specific sequences 05-32. Therefore the combined teachings of these references fails to teach or suggest these claims.

Claims 59, 63 and 67 (and any claims dependent thereon) limit the background probes to ones that have specific characteristics, e.g., reverse polarity nucleotide analogs, etc. The Examiner has not pointed to any location in the cited references where these specific characteristics are disclosed or suggested. Accordingly, the combined teaching of the references fails to teach or suggest these claims.

Finally, Claim 71 and the claims dependent thereon recite that the background feature must be a probe that does not hybridize to any target in the sample being assayed. The cited references teach the use of control probes that do not hybridize to the target for which they are designed, but one can envision target nucleic acids to which they would hybridize. For example, even though the type I and type II probes of Brink will not hybridize to the specific targets for which they are designed, one can envision target nucleic acids to which they would bind. As such, the combined teachings of the reference fail to render these claims obvious as well.

In sum, none of the cited references teach or suggest such background probes as recited in the pending claims. As such, none of the cited references teach or suggest the claimed invention and the rejection of Claims 50-68 and 71-74 as obvious under 35 U.S.C. § 103 (a) as being unpatentable over Dehlinger in view of Fodor, Blanchard and Brink may be withdrawn.

Conclusion

The applicant respectfully submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Gordon Stewart at (650) 485-2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 1.29.03

By: _____
Bret E. Field
Registration No. 37,620

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

50. (Amended) A hybridization assay comprising:

(a) contacting a sample of target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length must have no less than 70% sequence identity with a probe in order to hybridize to said probe with a collection of substrate bound probe nucleic acid features that includes at least one background nucleic acid feature that is an empirically observed inactive probe that does not hybridize to ~~its~~ a fully complementary fluorescently labeled target nucleic acid as determined in an assay wherein said probe is provided in an array that is contacted with said fluorescently labeled fully complementary target under said hybridization conditions;

(b) separating unbound target nucleic acids/label from said collection of probe nucleic acid features; and

~~(b)~~(c) detecting the presence of target nucleic acids hybridized to said collection of probe nucleic acid features;

wherein said method is further characterized by including a target nucleic acid labeling step prior to said detecting step(c).

Cancel Claim 53.

58. (Amended) A hybridization assay comprising:

(a) contacting a sample of target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length must have no less than 70% sequence identity with a probe in order to hybridize to said probe with a collection of substrate bound probe nucleic acid features that includes at least one background nucleic acid feature, wherein said at least one background feature is made up of a probe nucleic acid selected from the group consisting of SEQ ID NOS:

05 to 32;

b) separating unbound target nucleic acids/label from said collection of probe nucleic acid features; and

~~(b)~~(c) detecting the presence of target nucleic acids hybridized to said collection of probe nucleic acid features;

wherein said method is further characterized by including a target nucleic acid labeling step prior to said detecting step(c).

59. (Amended) A hybridization assay comprising:

(a) contacting a sample of target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length must have no less than 70% sequence identity with a probe in order to hybridize to said probe with a collection of substrate bound probe nucleic acid features that includes at least one background nucleic acid feature, wherein said at least one background feature is made up of a probe nucleic acid that is chosen from: (i) a probe nucleic acid that forms a stable intramolecular structure; (ii) a probe nucleic acid that comprises reverse polarity nucleotide analogs; and (iii) a probe nucleic acid that comprises abasic phosphodiesters;

b) separating unbound target nucleic acids/label from said collection of probe nucleic acid features; and

~~(b)~~(c) detecting the presence of target nucleic acids hybridized to said collection of probe nucleic acid features;

wherein said method is further characterized by including a target nucleic acid labeling step prior to said detecting step(c).

60. (Amended) A hybridization assay comprising:

(a) contacting a sample of detectably labeled target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length ~~to~~ must have no less than 70% sequence identity with a probe in order to hybridize to said probe with an array of probe nucleic acid features that includes at least one background nucleic acid feature that is an empirically observed inactive probe that does not hybridize to ~~its~~ a fully complementary fluorescently labeled target nucleic acid as determined in an assay wherein said probe is provided in an array that is

contacted with said fluorescently labeled fully complementary target under said hybridization conditions;

(b) separating non-hybridized target nucleic acids/label from said array; and

(c) detecting the presence of target nucleic acids hybridized to said array probe nucleic acid features;

wherein said method is further characterized by including a target nucleic acid labeling step prior to said detecting step(c).

64. (Amended) A hybridization assay comprising:

(a) contacting a sample of target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length must have no less than 70% sequence identity with a probe in order to hybridize to said probe with an array of probe nucleic acid features that includes at least one background nucleic acid feature that is an empirically observed inactive probe that does not hybridize to its fully complementary target nucleic acid as determined in an assay wherein said probe is provided in an array that is contacted with said fluorescently labeled fully complementary target under said hybridization conditions;

(b) separating non-hybridized target nucleic acids from said array;

(c) detectably labeling target nucleic acids hybridized to said array of probe nucleic acid features;

(d) separating unbound label from said array; and

~~(d)~~(e) detecting the presence of target nucleic acids hybridized to said array of probe nucleic acid features.

66. (Amended) A hybridization assay comprising:

(a) contacting a sample of target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length must have no less than 70% sequence identity with a probe in order to hybridize to said probe with an array of probe nucleic acid features that includes at least one background nucleic acid feature, wherein said at least one background feature is made up of a probe nucleic acid selected from the group consisting of SEQ ID NOS: 05 to 32;

(b) separating non-hybridized target nucleic acids from said array;

(c) detectably labeling target nucleic acids hybridized to said array of probe nucleic acid features;

(d) separating unbound label from said array; and

~~(d)~~(e) detecting the presence of target nucleic acids hybridized to said array of probe nucleic acid features.

67. (Amended) A hybridization assay comprising:

(a) contacting a sample of target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length must have no less than 70% sequence identity with a probe in order to hybridize to said probe with an array of probe nucleic acid features that includes at least one background nucleic acid feature, wherein said at least one background feature is made up of a probe nucleic acid that is chosen from: (i) a probe nucleic acid that forms a stable intramolecular structure; (ii) a probe nucleic acid that comprises reverse polarity nucleotide analogs; and (iii) a probe nucleic acid that comprises abasic phosphodiesters;

(b) separating non-hybridized target nucleic acids from said array;

(c) detectably labeling target nucleic acids hybridized to said array of probe nucleic acid features;

(d) separating unbound label from said array; and

~~(d)~~(e) detecting the presence of target nucleic acids hybridized to said array of probe nucleic acid features.

71. (Amended) A hybridization assay comprising:

(a) contacting a sample of target nucleic acids under hybridization conditions where a target nucleic acid of 14 nucleotides in length must have no less than 70% sequence identity with a probe in order to hybridize to said probe with a collection of substrate bound probe nucleic acid features that includes at least one background nucleic acid feature made up of background probes that do not selectively bind to any of said target nucleic acids;

(b) washing said contacted array to remove unbound target nucleic acids/label from said array; and

~~(b)~~(c) detecting the presence of target nucleic acids hybridized to said

collection of probe nucleic acid features;

wherein said method is further characterized by including a target nucleic acid labeling step prior to said detecting step(c).

Cancel Claim 74.